

REMARKS

Claims 1, 3 and 6-28 are pending after entry of the amendments set forth herein, claims 1, 3, 6, 19, 22 and 25 are under consideration.

Claims 1-3, 6, 19, 22 and 25 have been amended.

Please replace the claims with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

35 USC §112 FIRST PARAGRAPH

Claims 1, 3, 6 19, 22 and 25 have been rejected under 35 USC §112 first paragraph. Applicants respectfully submit that the presently claimed invention is enabled by the specification.

The Office Action alleges that the identity of the compound to be screened is unpredictable and therefore the specification lacks reasonable enablement for a method of identifying a compound that negatively regulates the interactions described in the specification.

The rejection appears to be based on a misunderstanding of the nature of the claimed screening method. Advances in cellular biology in recent years have provided a wealth of information on protein-protein interactions that are involved in a range of cellular processes and are potential targets for therapeutic intervention. Indeed, the present assignees, (KuDOS Pharmaceuticals Ltd) specialize in the development of targets in the field of DNA repair.

Protein-protein interactions of the type identified in the present specification are therefore the subject of considerable academic research and commercial interest. The interest arises because the interaction provides a new and useful tool for the development of therapeutic compounds for the treatment of diseases in which DNA repair systems are an underlying problem.

The present claims thus set out a screening method which those of skill in the art can use in the discovery or identification of compounds that are useful for control of DNA repair. It is not a point of novelty for the present invention as to the particular compound used in the assay.

Screening methods of the kind recited are in themselves known in the art. The present invention provides a novel screening method by virtue of the presence of the XRCC4, DNA ligase IV and DNA-PK α /Ku polypeptides, whose interaction was unknown prior to the present invention. The specification does suggest a number of potential inhibitors that could be tried, based upon, for example, fragments of these proteins. However this list is clearly not exclusive and those of skill in the art are free to use any compound of their choice in such a screening method.

Commercial available libraries of compounds are widely available in the art and are sold for use in screening assays of the present type. By way of example, extracts of the websites of some of the many companies that specialize in the provision of chemical libraries are attached, as follows:

Key Organics Ltd, (Cornwall, UK). The company advertises a novel organic chemistry for biological screening. The company states that it has been active since 1986.

ChemDiv, Inc (Moscow, Russia; San Diego, USA). Advertises a broad source of novel relevant molecules for, e.g., high throughput screening. The small molecule collection includes small molecule compounds and pure natural compounds as well as plant and fungal extracts.

Evotec OAI (Oxford, UK). The company advertises a drug discovery library totalling more than 125,000 compounds.

Tripos, Inc. (St. Louis, USA). Advertises a library of 80,000 compounds for screening for biological activity for use in the pharmaceutical, biotechnological and life science industries.

ChemStar (Moscow, Russia). Offers organic compounds for High Throughput Screening in the pharmaceutical and biotechnology industry.

The purpose of screening methods of the type claimed is to provide the skilled person with a means to examine large numbers of compounds (for example, using a commercial library as described above) so as to be able to discover new and useful products that allow new treatments of disease to be developed. It is a characteristic feature of such screening methods that a large number of different compounds will need to be screened in order to identify a few compounds with the desired activity.

Given that a large number of test compounds will be screened by methods of the type described in the specification, rejection of claims to screening methods for the sole reason that the term 'compound' does not satisfy the requirements of 35 USC§112 first paragraph would render any screening method unpatentable and would represent a *de facto* bar on the

patentability of screening methods, which may have great commercial value. It is respectfully submitted that there is no such bar in US law.

A simple search for issued US patents with claims containing the terms 'screening' and 'compound' identified 691 issued patents in the last 5 years (copy of search enclosed). This is further evidence that, contrary to the Examiner's assertion, the broadly defined term 'compound', in the context of a screening method, meets the requirements of 35 USC§112 first paragraph.

It is further noted that in the Trilateral Project B3b Report on Comparative study on biotechnology patent practices (Theme 'Comparative study on 'reach-through claims' (Nov 5-9 2001)), no rejections were raised by the USPTO (or any of the other offices) to the use of the term 'candidate compound' in claims to screening methods (claim 2 of cases 1, 2, 3, and 4).

The Examiner has analyzed the requirements of 35 USC §112 first paragraph by weighing up the factors set out in *in re Wands*. However, in misunderstanding the nature of the invention, these factors have been misapplied to arrive at an erroneous conclusion. In fact, for the reasons set out below, a consideration of these factors shows that the disclosure of the specification satisfies the requirements of 35 USC §112 enablement requirement and no undue experimentation is required to practice the invention.

a) The nature of invention/scope of claims

The Examiner suggests that, because the genus of 'compounds' is broad, it is unpredictable. This is not the case. Whilst a broad genus of compounds can be screened using the present methods, no element of unpredictability is introduced into the claimed screening methods by the breadth of this genus. The screening method either shows that the compound is active or it shows that the compound is inactive. These are the only two outcomes and all members of the genus of 'compounds' will be found to be either inactive or active by the present methods. This is totally predictable. A skilled person can select any member of the genus of 'compounds' in the certainty that the screening method will identify the compound as either active or inactive.

The Examiner's comments on the '*unpredictability of the outcome of the screening method*' are therefore incorrect. The outcome of the screening method is entirely predictable and shows either activity or inactivity for any given compound.

In order to be screened by the present methods, the compound is not required to possess any particular properties, attributes or features: a compound of any structure may be subjected to a screening method of the invention. As no function or activity is required of the

compound in order to produce one or other of the two possible outcomes (i.e. active or inactive), there is no requirement for any degree of prediction of properties or structure before the method is performed and no 'pre-selection' is required. This is, of course, the whole point of a screening method. If a skilled person could predict in advance which compounds would be identified as active using the screening method, there would be no point in actually performing the method.

The skilled person can therefore work the invention on any member of the genus of 'compounds' without any undue experimentation – the artisan simply needs to pick a compound and perform the assay. The Examiner suggests that the skilled person would face problems in synthesizing or producing compounds that are suitable for screening by the present methods. However, knowledge of chemical synthesis or modification is irrelevant to present invention. A skilled person simply takes a compound and ascertains, using a method of the invention, whether the compound is active or inactive. There is no need to design, synthesize or modify a compound to generate any particular activity or function – a method performed in accordance with the invention may equally identify a compound as inactive. As discussed above, screening methods represent an alternative approach to rational drug design methods. Compounds are screened without any prior analysis, prediction or design and the small proportion identified as 'hits' (i.e. showing some activity) are then subjected to further optimization and development.

The predictability and complexity of the present screening methods are not affected by the interaction of the XRCC4-DNA ligase IV complex with DNA PKcs/Ku. A compound that is found to inhibit any one of the DNA repair protein interactions described in the specification is likely to have a consequent effect on the mechanism of DNA repair and is therefore useful in the development of therapeutics. It is irrelevant to the skilled person performing the assay whether the particular interaction that is targeted by the compound is a bimolecular, ternary or quaternary interaction event. The benefit of the invention i.e. the identification of a useful lead compound for the development of therapeutics can be achieved without any further investigation.

In summary, the broad genus encompassed by 'compound' does not automatically mean that the term is unpredictable or unenabled. In the context of a screening method, the broad definition is entirely appropriate and any limitation to a particular compound or class would be wholly arbitrary. The nature of the invention is therefore such that the scope of the term 'compound' is entirely appropriate.

b) Predictability of the art

Contrary to the Examiners assertion, the use of the term 'compound' does not render the screening method unpredictable. Any compound may be screened by a method of the invention and identified as being either active or inactive. This is wholly predictable and every member of the genus 'compound' will fall into one of these two categories. The use of a broadly defined term is therefore accurate and appropriate.

As described above, no pre-screen prediction of activity is required and indeed, the whole point of a screening method is to obviate the need for such prediction.

Given that the screening of large numbers of bio- and/or organic molecules is routine in the art (as evidenced by the commercial library information filed herewith), it is not clear what additional factual indicia might be used to further support the applicant's position. Furthermore, given the routine nature of such screening, it is respectfully submitted that the onus is on the Examiner to provide factual indicia of the unpredictability of such a method, should the present rejection be maintained.

c) State of the prior art

The Examiner suggests that, because large numbers of variant compounds might be screened by the present methods, the methods themselves would be numerous and variant. This is not the case. A variety of well-established assay formats are available in the art and each of these formats is suitable for screening large numbers of 'variant' compounds. The skilled person would have no difficulty in screening a 'large and variant' number of compounds using a single screening method.

Many examples of the use of a single screening method to screen a large number of compounds are found in the art. An example of a review of such methods is Lawrence JR, et al *High Throughput Screening*. New York: JRL Press, 1995. Examples of papers which describe methods for screening large numbers of compounds include Umezawa Y. 'Assay and screening methods for bioactive substances based on cellular signaling pathways' J Biotechnol 2002 Feb;82(4):357-70, Boute N et al 'The use of resonance energy transfer in high-throughput screening: BRET versus FRET' Trends Pharmacol Sci 2002 Aug;23(8):351-4, Gonzalez JE, Negulescu PA. 'Intracellular detection assays for high throughput screening' Curr Opin Biotechnol 1998 Dec;9(6):624-31, Kay BK, Paul JI 'High-throughput screening strategies to identify inhibitors of protein-protein interactions' Mol Divers 1996 Feb;1(2):139-40. The applicant would be happy to provide copies of any or all of these references should the

Examiner require it. Further evidence that a single assay format may be used to screen a large number of test compounds is found in paragraph 7 of the Jackson declaration (of record).

The Examiner further suggests that using the two-hybrid assay format to perform screening methods of the invention would require undue experimentation. However, two-hybrid assays are standard in the art and have been successfully employed with many different proteins (see for example, Cagney G et al '*High-throughput screening for protein-protein interactions using two-hybrid assay*' Methods Enzymol 2000;328:3-14, Gietz RD & Woods RA '*Screening for protein-protein interactions in the yeast two-hybrid system*' Methods Mol Biol 2002;185:471-86). There is simply no basis for the assertion that it would be problematic to employ the two-hybrid assay for the present screening methods. Indeed the evidence of the art is that this format is particularly suitable for the present methods. Grawunder et al (1997) Nature 388 492-495 (of record) describes experiments in which the interaction of XRCC4 and DNA ligase IV is investigated using a two-hybrid assay. Producing the appropriate fusion proteins and expressing them in yeast was apparently straightforward and no particular problems, such as protein degradation, were encountered.

As is well known in the art, the yeast two-hybrid screen format may equally be applied to interactions involving three components. For example, if protein A interacts with protein B, and protein B interacts with protein C, protein A may be linked to a DNA binding domain and protein C may be linked to a transcriptional activation domain. Transcriptional activation will only ensue when proteins A, B and C are present, as protein B forms a bridge between proteins A and C. In this screen format, inhibition of either of the two protein interactions (i.e. A/B or B/C) will result in loss of two-hybrid interaction, and thereby inactivation of whatever reporter system is being used.

In the light of McElhinny et al Mol Cell Biol (2000) 20 2996-3003 (which is not prior art to the present application), the Examiner further suggests that dsDNA is an essential component of screening methods for therapeutically active compounds.

Whilst DNA has an enhancing effect on these interactions, XRCC4, DNA ligase IV and DNA-PKcs/Ku interact with each other inherently in the absence of DNA. This is shown in the present specification on page 68 line 25 to page 70 line 3 and in McElhinny et al in Figure 3b lanes 3 and 5. In order to identify modulators of the interactions between these proteins, a screening method does not require the presence of DNA, although of course, this is not excluded. Although the strength of the interactions may be enhanced in the presence of DNA, the interactions between the protein components themselves are not fundamentally changed in

the presence of DNA and their disruption by test compounds can be determined equally in the presence or absence of DNA. DNA is not required in order to model the XRCC4/DNA ligase IV/DNA-PKcs/Ku interactions in a physiologically relevant manner.

The interactions between XRCC4, DNA ligase IV and DNA-PKcs/Ku are shown to be an important part of the mechanism of DNA repair and disruption of these interactions by modulating compounds will have a consequent effect on DNA repair activity within cells.

Thus, compounds identified by screening methods in the absence of DNA are highly applicable to the treatment of DNA repair related disease states.

The specification therefore provides a complete teaching of the present invention and no additional information or skills are required by the skilled artisan in order to practice the present methods.

d) Quantity of experimentation necessary

Screening methods for compounds that modulate protein/protein interactions are well known in the art and a variety of commonly used formats are available (see para 7 of the Jackson declaration, Jan 2002; of record).

No prediction need be made about the compounds to be screened and the outcome of the assay is predictable. The art is full of examples of screening methods based on protein/protein interactions – these are predictable and well understood and it is a matter of routine for a skilled person to plug two proteins into a screening method format, once they have been shown to interact. The specification itself discusses various known screening formats on page 28 line 24 to page 32 line 4.

The Examiner asserts that a skilled person is required to carry out a large body of pre-search for a group of compounds that are obtainable or producible. This is not the case. No pre-selection or prediction of test compounds is required – any compound may be used in a method. The compound must clearly be obtainable/producible by a skilled person or else the skilled person could not use it in the method, but this does not introduce undue experimentation – the skilled person simply uses that which is obtainable without further experimentation or does not use non-obtainable compounds, again without further experimentation. There is no requirement for disclosure of a synthetic route to every conceivable compound in order to claim the use of a compound in an assay.

The level of experimentation required to work the invention is therefore routine and predictable.

e) Relative skill of those in the art.

The Examiner suggests that the level of skill is high and requires a large team of experienced workers because the predictability of results is highly variable.

However, screening methods for modulators of protein/protein interactions are well known in the art. It is a matter of routine to 'plug' known proteins into any one of a number of test formats to undertake such a screen, once it is established that the proteins interact. This is within the realm of a single technician and does not require a large and expert team.

As explained above, the results of the screening method on a member of the genus compound are highly predictable - the method will either indicate activity or inactivity. There is no requirement for activity prediction, synthesis or mutagenesis in order to perform the method. The level of skill and experimentation required to work the invention in the light of the disclosure of the specification is therefore minimal.

The Examiner notes that Grawunder et al (1997) Nature 388 492-495 (of record: not prior art to the present application), indicates that the activity of DNA ligase IV is increased when it is co-expressed with XRCC4. However, this does not affect the ability of the skilled person to perform screening methods. The skilled artisan is familiar with basic scientific methodology and is able to design and set up control experiments. It is standard scientific practice for the conditions employed in control experiments (i.e. in the absence of test compound) to be the same as those in the actual experiments (i.e. in the presence of test compound) in order for meaningful results to be obtained. The mere fact that ligase activity may vary, depending on conditions, makes no difference at all to the present methods, as long as these conditions are kept the same in both test and control experiments.

The Examiner indicates that *'selection of compounds out of such a compound library would not be predictable which in turn renders the method outcome for identifying inhibitory candidate compounds unpredictable'*. However, as stated above, any (or indeed every) compound in a compound library may be screened using methods of the invention without any 'selection' or 'prediction' step. The results of the method are entirely predictable: a given compound either has or does not have inhibitory activity. The experimentation level required is therefore entirely routine.

The Examiner further indicates that the application does not provide teaching or guidance as to how to select and make variants or mutant compounds. However, although methods of making peptide mutants and variants are well known in the art, this is irrelevant to

consideration of the invention. The artisan does not need to select particular subject compounds from different compound classes. Instead, the artisan simply screens all available compounds. Each compound screened is found to be either active or inactive using a method of the invention. Selecting or making variant or mutant compounds has no bearing on this screening, in the same way that constructing and wiring up an oven has no bearing on a method of baking a cake.

In summary, an analysis of the factors set out in *in re Wands* indicates that the present claims are fully described by the present specification and meet the requirements of 35USC112 first paragraph. Reconsideration of the rejection is respectfully requested.

Claims 1 and 6 have been rejected under 35 USC §112 second paragraph.

Claim 1 has been amended to emphasize that the term 'binding' refers to the 'binding of XRCC4 and said one or more components'.

Claim 6 has been amended to emphasize that DNA-PKcs alone is able to phosphorylate XRCC4.

The wording of claims 1 and 6 meets the requirements of 35. USC 112 second paragraph. Withdrawal of the Examiner's rejection is respectfully requested.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

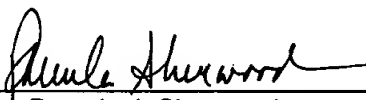
Atty Dkt. No.: MEWE-005

USSN: 09/341,505

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number MEWE-005.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 30, 2002

By: 
Pamela J. Sherwood
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A screening method for identifying a compound [X] which inhibits the binding between XRCC4 (XR-1 Cell Complementing 4) and DNA ligase IV, or XRCC4 and DNA-PK_{CS}/Ku (DNA-dependent Protein Kinase catalytic subunit/Ku) , or XRCC4, DNA ligase IV and DNA-PK_{CS}/Ku, the method comprising the steps of:

(i) contacting XRCC4 with a test compound [X] and one or more components selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku;
under conditions wherein, in the absence of said test compound [X] being a compound which inhibits [an inhibitor of] binding of XRCC4 to said one or more compounds, said XRCC4 binds to said one or more components [selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku]; and

(ii) determining binding between said XRCC4 and said one or more components [selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku];

wherein reduction or abolition in binding between said XRCC4 and said one or more components [selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku being] is indicative that said test compound is a compound [X] which inhibits binding between XRCC4 and DNA ligase IV, or XRCC4 and DNA-PK_{CS}/Ku or XRCC4, DNA ligase IV and DNA-PK_{CS}/Ku.

3. (amended) A screening method for identifying a compound [X] which inhibits DNA ligase IV activity, the method including the steps of:

(i) [bringing into contact] contacting DNA ligase IV, XRCC4 and a test compound [X];
and

(ii) determining DNA ligase activity in the presence and the absence of test compound X,

wherein a decrease in the activity in the presence relative to the absence of test compound [X being] is indicative that said test compound [X] is a compound which inhibits the activity of DNA ligase IV.

6. (amended) A screening method comprising

(i) contacting a test compound [X], DNA-PK_{CS}/Ku and XRCC4; and

(ii) determining phosphorylation of said XRCC4 in the presence and the absence of the test compound [X];

wherein a decrease in phosphorylation in the presence relative to the absence of the test compound [X being] is indicative that said test compound [X] inhibits the phosphorylation of XRCC4 by DNA-PK_{CS}[/Ku].

19. (amended) A method comprising obtaining a compound [X] which inhibits the binding between XRCC4 and DNA ligase IV, or XRCC4 and DNA-PK_{CS}/Ku, or XRCC4 and DNA ligase IV and DNA-PK_{CS}/Ku, employing a method according to claim 1; and, formulating said compound [X] into a composition which comprises a pharmaceutically acceptable excipient.

22. (amended) A method comprising obtaining a compound [X] which inhibits DNA ligase IV activity employing a method according to claim 3 and formulating said compound [X] into a composition which comprises a pharmaceutically acceptable excipient.

25. (amended) A method comprising obtaining a compound [X] which inhibits DNA-PK_{CS}/Ku phosphorylation of XRCC4 employing a method according to claim 6 and formulating said compound [X] into a composition which comprises a pharmaceutically acceptable excipient.



USPTO PATENT FULL-TEXT AND IMAGE DATABASE

[Home](#)[Quick](#)[Advanced](#)[Pat Num](#)[Help](#)[Next List](#)[Bottom](#)[View Cart](#)

Searching 1996-2002...

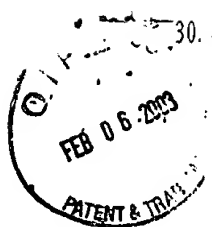
Results of Search in 1996-2002 db for:

ACLM/(screening AND compound): 691 patents.

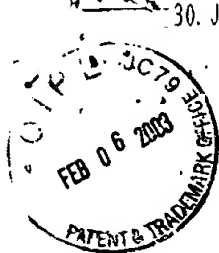
Hits 1 through 50 out of 691

[New Search](#)[Refine Search](#)[Refine Search](#) aclm/(screening and compound)

PAT. NO.	Title
1 6,492,499	Human pancreatitis-associated protein
2 6,492,124	Trans activated signal transduction pathways in osteoclasts
3 6,492,108	Delta-6 desaturase homologs
4 6,492,107	Process for obtaining DNA, RNA, peptides, polypeptides, or protein, by recombinant DNA technique
5 6,489,535	Non-mammalian transgenic animal having an adult onset neurodegenerative phenotype
6 6,489,444	Human lysyl hydroxylase-like protein
7 6,489,125	Methods for identifying chemical compounds that inhibit dissociation of FKBP12,6 binding protein from type 2 ryanodine receptor
8 6,486,300	Human nm23-like protein
9 6,486,105	Heat activated durable conditioning compositions comprising C3 to C5 monosaccharides, and methods for using same
10 6,485,919	Human metabotropic glutamate receptors, nucleic acids encoding same and uses thereof
11 6,485,899	Anti-bacterial methods and materials
12 6,482,587	Methods to inhibit or enhance the binding of viral DNA to genomic host DNA
13 6,479,729	Mouse model for ocular neovascularization
14 6,479,241	High throughput screening of the effects of anti-cancer agents on expression of cancer related genes in various cell lines
15 6,479,064	Culturing different cell populations on a decellularized natural biostructure for organ reconstruction
16 6,475,746	Method of obtaining a composition comprising a 5-HT1D selective compound
17 6,475,485	Two novel human cathepsin proteins
18 6,472,195	Human kallikrein



- 19 6,472,165 Modulatory binding site in potassium channels for screening and finding new active ingredients
- 20 6,472,141 Kinase assays using polycations
- 21 6,471,959 Human transferase
- 22 6,471,949 Compositions comprising at least one UV screening agent and at least one flavylum salt which is unsubstituted in position 3, for coloring the skin, and uses thereof
- 23 6,470,167 Heating roller for fixing a toner image and method of manufacturing the same
- 24 6,468,756 Methods of identifying compounds that bind to SNORF25 receptors
- 25 6,468,736 High efficiency cell analysis system and high throughput drug screening system
- 26 6,465,619 Transducin beta-1 subunit
- 27 6,465,281 Method of manufacturing a semiconductor wafer level package
- 28 6,465,258 FXR receptor-mediated modulation cholesterol metabolism
- 29 6,461,822 Methods of screening compounds for their ability to inhibit the production of inflammatory cytokines
- 30 6,461,815 Antibacterial agents and methods of screening for the same
- 31 6,458,847 Method for screening for drugs useful in inhibition of polymerization of a beta- and tau peptides
- 32 6,458,575 Cyclophilin-type peptidyl-prolyl CiS/trans isomerase
- 33 6,458,538 Methods of assaying for compounds that inhibit premature translation termination and nonsense-mediated RNA decay
- 34 6,455,755 Leukotriene B4 receptor transgenic mice
- 35 6,455,754 GENOMIC DNA FRAGMENTS CONTAINING REGULATORY AND CODING SEQUENCES FOR THE .beta.2-SUBUNIT OF THE NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR AND TRANSGENIC ANIMALS MADE USING THESE FRAGMENTS OR MUTATED FRAGMENTS
- 36 6,455,323 Anti-bacterial methods and materials
- 37 6,451,548 Methods for screening for specific inhibitors of trap and identifying compounds for treatment of diseases or conditions resulting in increased bone resorption using activated TRAP
- 38 6,448,376 Transcription factor-E2F-5
- 39 6,448,097 Measure fluorescence from chemical released during trim etch
- 40 6,448,011 DNA encoding human alpha 1 adrenergic receptors and uses thereof
- 41 6,448,006 Methods and compositions for reducing bacterial tolerance to antibacterials disinfectants and organic solvents
- 42 6,447,994 Production of replicative hepatitis C virus
- 43 6,447,661 External material accession systems and methods
- 44 6,444,431 Angiostatin receptor
- 45 6,444,419 TMPRSS2 is a tumor suppressor
- 46 6,441,152 Methods, kits and compositions for the identification of nucleic acids electrostatically bound to matrices
- 47 6,440,659 Inhibitors of retroviral protease as inducers of reversible insulin resistance in vitro and in vivo
- 48 6,437,215 SR-BI and ApoE knockout animals and use thereof as models for atherosclerosis and heart attack
- 49 6,436,683 Human nucleic acid methylases
- 50 6,436,656 Method for screening a test compound for potential as an immunosuppressive drug

candidate

[Next List](#)[Top](#)[View Cart](#)[Home](#)[Quick](#)[Advanced](#)[Pat Num](#)[Help](#)